Treatment of Angina

Learning Objectives

By the end of the module you should be able to:

1. Describe the pathophysiology of the three major forms of angina.
2. List the strategies for relief of angina.
3. Contrast the therapeutic & adverse effects of nitrates, beta-blockers & calcium channel blockers used for treating angina.
4. Explain how glucagon can be used to treat beta-blocker overdose.
5. Explain the benefits of combining a nitrate with a beta-blocker or a calcium channel blocker.
6. Explain the danger of combining a nitrate with sildenafil.
7. Explain the current standard of care regarding the use of fibrinolytics & other drugs (e.g. MONA) in treating **Unstable Angina**, **NSTEMI** & **STEMI**.

Drugs:

- **Nitrates:** nitroglycerin, isosorbide dinitrate
- **Beta Blockers:** propranolol, metoprolol, atenolol
- **Calcium Channel Blockers:** nifedipine, verapamil, diltiazem
- **Metabolism Modifiers:** ranolazine
- **Related Drugs:** glucagon, sildenafil
- **Unstable Angina Rx:** Morphine, Oxygen, Nitroglycerin, Aspirin (**MONA**)

Abbreviations:

- **STEMI** - ST elevated Myocardial Infarction
- **NSTEMI** – Non-ST elevated Myocardial Infarction

The Case of Dr. Strangelove

Dr. Victor Strangelove, a 77 year old professor, has been taking sublingual nitroglycerine PRN for exercise-related chest pain (angina) for the past 2 years. Recently metoprolol was also added to his daily drug regimen. On a followup visit 3 weeks later, Victor states that his need for nitroglycerin has been reduced since he started taking the beta blocker.

1. **What is the most common pathophysiological mechanism underlying exercise-induced angina?**
2. **How does nitroglycerine alleviate his angina?**
3. **Why is nitroglycerine taken sublingually?**
4. **How does metoprolol reduce angina?**
5. **Why did metoprolol reduce his need for taking nitroglycerin?**

Background Pathophysiology

- Angina Pectoris is a form of paroxysmal (sudden onset) chest pain that is felt beneath the sternum, and commonly radiates down the left arm &/or shoulder. It can also radiate or originate in the neck or upper back as well.
- Angina is a cardinal sign of coronary artery disease (ischemic heart disease).
- Angina is caused by an **imbalance of O_2 supply vs. demand**, resulting in myocardial ischemia (Figure 1).

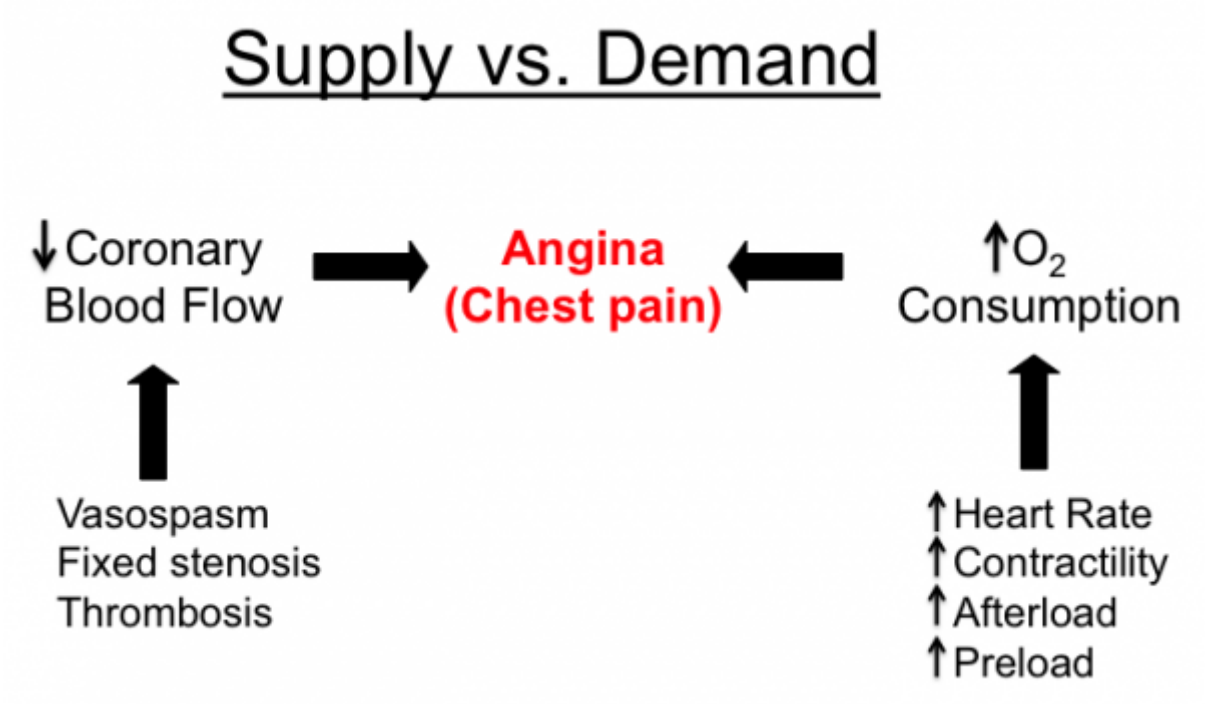

Figure 1. Different parameters that can contribute to producing angina. A variety of conditions can result in a reduction in coronary blood supply, including a stable or fixed stenosis caused by an atherosclerotic plaque on the wall of a large coronary artery (the most common cause in **stable** or **exertional angina**), vasospasm of a diseased vessel wall (in **Prinzmetal's** or **vasospastic angina**), a much more rare cause, or occlusion of an artery by platelets adhering to a rupturing plaque, or damaged vessel wall (**unstable angina**). Various cardiovascular parameters including heart rate, contractility (the work of the heart), and parameters that affect the work of the heart (afterload & preload) can affect O_2 demand and cause angina. Each parameter is a potential target for treatment.

STABLE ANGINA (Typical or Exertional Angina)

- The most common form of angina (**stable or exertional angina**) is **caused by the formation of atherosclerotic plaques in large epicardial coronary arteries**, resulting in stenosis. Distal resistance vessels are usually plaque free, and can adjust their vasomotor tone in response to metabolic needs.
- When a stenosis develops to the extent that the lumen diameter is narrowed by ~70%, blood flow when the body is at rest will be normal and sufficient, but maximal blood flow during exertion will be reduced even when distal resistance vessels become fully dilated. In this situation, coronary flow will be inadequate and ischemia with chest pain results (Rhee et al, 2011). [If you want a refresher on coronary artery stenosis and O_2 supply vs. demand you may want to listen to this

https://www.khanacademy.org/science/health-and-medicine/circulatory-system-diseases/heart-disease-and-stroke/v/stenosis-ischemia-and-heart-failure].

Epidemiology:

- The most common patients with stable angina are men >50 years of age, or postmenopausal women >60 (Sheikh et al, 2007; Antman et al, 2012).
- The common risk factors that predispose patients to atherosclerosis, CV disease & exertional (stable) angina include (Sheikh et al, 2007; Rhee et al, 2011):
  - Family history of coronary artery disease (e.g. MI) or heart disease (1st degree relative, man <55 yrs, woman <65 yrs)
  - Male gender
  - Hypertension
  - Hyperlipidemia
  - Metabolic syndrome
  - Obesity
  - Diabetes
  - Cigarette smoking
  - Heart murmurs
  - Sedentary lifestyle
  - Drug use: e.g. stimulants such as amphetamines, cocaine, ephedra, migraine medications (sumatriptan)

Clinical Presentation:

- The sensation of chest pain typically occurs in regions of the body (chest, left arm & neck) that share a common spinal cord origin of sensory neurons with the heart (Lee, 2012).
- The pain is often described as being a “tightness”, “heaviness” or “pressure like” feeling in the chest, and not a sharp pain.
- Patients may place a clenched fist over their sternum when describing their symptoms (the Levine sign).
- Pain always lasts more than a few seconds, but rarely more than 5-10 minutes.
- The pain does not vary significantly with inhalation or exhalation (Rhee et al, 2011).
- Common triggers of exertional angina include the 4 “E's”:
  - **Exertion**
  - **Emotional Stress**
  - **Exposure to cold or hot/humid weather**
  - **Eating a heavy meal**
    - The relative risk for an Acute Coronary Syndrome is significantly elevated during the first hour after a large fatty meal. The mechanisms are still poorly understood, but may result from a combination of triglyceride- or lipoprotein-induced endothelial dysfunction, microcirculatory obstruction by large platelet aggregates, and/or increases in systolic blood pressure (Lipovetzky et al, 2004)
- Exertional angina occurs more frequently in the morning due to diurnal **increases in sympathetic tone** (Podrid, 2012).
- **Exertional angina most commonly produces ST segment depression in the ECG** (Figure 2)
- However, **T wave changes (e.g. inverted T waves) can also occur**
- **An elevated ST segment can also occur** if there is sufficiently severe transmural myocardial ischemia. However, in contrast to an MI, ST segment & T wave deviations will normalize in parallel

with resolution of a patients symptoms at the end of the anginal episode (Rhee et al, 2011).

VASOSPASTIC ANGINA (Prinzmetal's Angina)

- A small fraction of patients have episodes of **variant (or Prinzmetal) angina** caused by **focal coronary artery vasospasm** in either the presence or absence of atherosclerotic plaques.
- The mechanisms involved are still poorly understood, but are believed to involve both increased smooth muscle hyperreactivity, and endothelial dysfunction of large epicardial vessels.
- **Spasm can typically be precipitated by acetylcholine, methacholine, ergonovine or hyperventilation** (Ternay et al, 2007; Rhee et al, 2011; Pinto et al, 2013). Due to the risks involved, these tests are done only when the diagnosis of variant angina is suspected, but not firmly established (e.g. typically in a cath lab, and performed by experienced teams)(Pinto et al, 2013).
- **Attacks occur more commonly at night when vagal tone is higher**, suggesting that an abnormal response to parasympathetic tone is involved in triggering attacks. Serotonin, histamine & dopamine have also been found to be able to provoke attacks (Pinto et al, 2013).

Epidemiology:

- Variant angina is more common in patients from Japan compared to Caucasians.
- It occurs more commonly in younger patients (**under the age of 50**) compared to more elderly patients.
- Patients typically have fewer CV risk factors compared to those suffering from exertional angina, with the exception of **cigarette smoking** which has been identified as **a major risk factor for coronary vasospasm** (Sugiishi & Takatsu, 1993; Pinto et al, 2013).
- **Cocaine** may precipitate vasospasm (Pinto et al, 2013)

Clinical Presentation:

- Attacks of variant angina **occur predominantly at rest (when vagal tone is higher), most frequently between midnight and early morning**.
- Each episode of chest pain generally lasts 5 to 15 minutes, and has many symptoms very similar to exertional angina (e.g. nausea, sweating, dizziness, dyspnea, and palpitations) (Pinto et al, 2013).
- When detected during the recording of an ECG, is associated with **ST segment elevation** (vs depression) in multiple leads (Pinto et al, 2013).

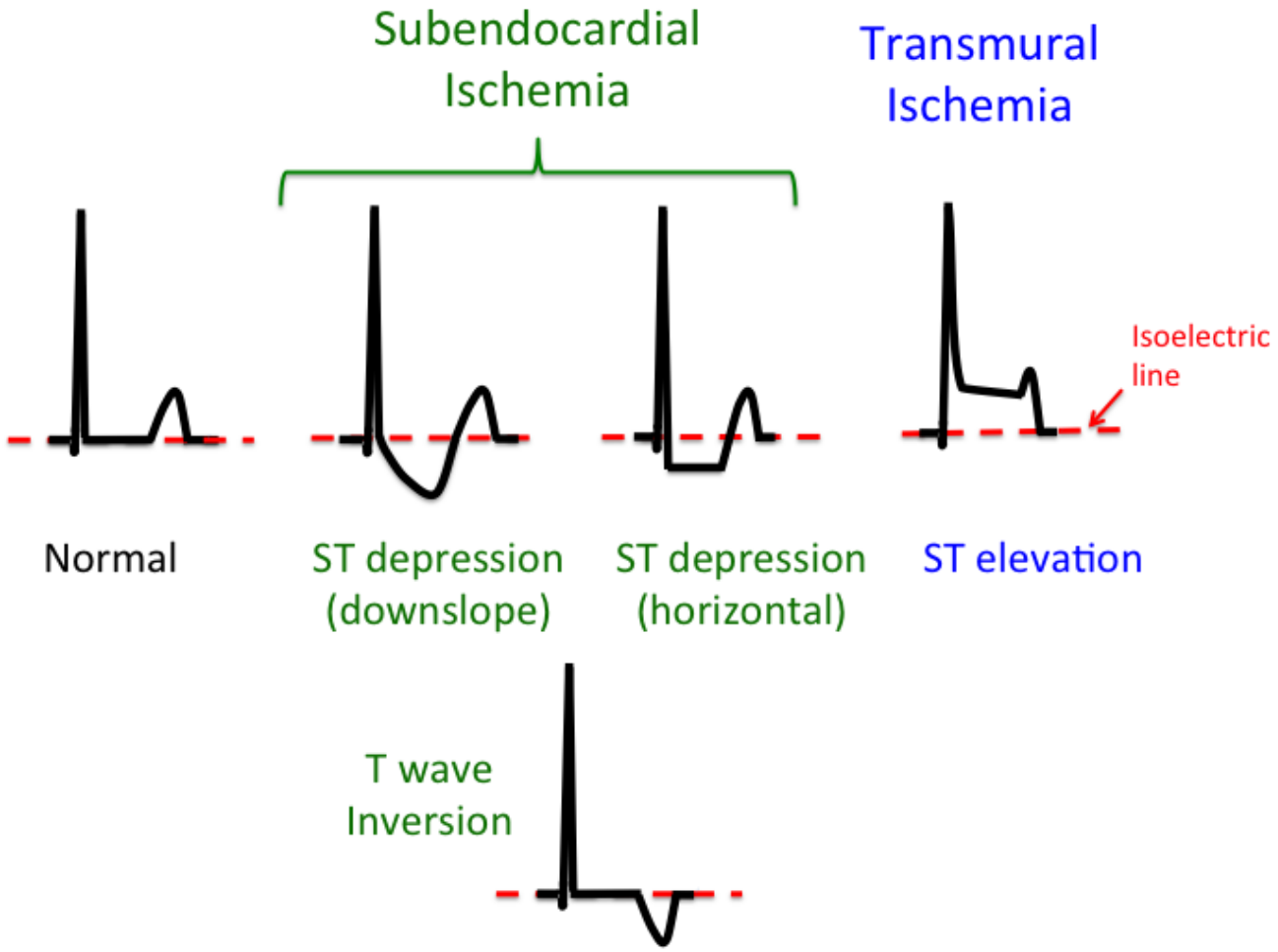

Figure 2. Common ECG patterns associated with myocardial ischemia. Transient subendocardial ischemia commonly results in ST segment depression (downsloping or horizontal), or T wave inversion. Transmural ischemia or infarcts result in ST elevation. Modified after Rhee et al, 2011).

UNSTABLE ANGINA

- Unstable angina (UA) results from **rupture of an atherosclerotic plaque, platelet aggregation, formation of a thrombus**, and possible unopposed vasoconstriction resulting in increased ischemic symptoms.
- UA differs from a non-ST segment MI only in that the extent of ischemia is not sufficient to produce death of heart muscle with release of cardiac enzymes into the blood stream. Nevertheless it is considered a medical emergency because it can rapidly evolve into a full Non-ST Segment MI (NSTEMI) or a transmural ST Segment Elevated MI (STEMI).

Clinical Presentation:

Unstable angina typically presents in one of 3 ways (Rhee et al., 2011b):

- a sudden **increase in the frequency, intensity or duration (e.g. >20 minutes) of ischemic episodes**
- anginal episodes **occur at rest, without provocation, in a patient with a history exertional angina**

- a new onset of severe anginal episodes in a patient with no prior history of angina

Summary On the 3 Types of Angina:

1. **Typical (exertional or classic) angina**
   - **the most common form of angina (~90%)**
   - results from coronary insufficiency due to partial vessel occlusion caused by atherosclerosis (Figure 3).
   - attacks usually **occur during exercise** (climbing stairs, etc) when oxygen demand exceeds oxygen supply.
   - Symptoms typically last 2-15 minutes, and are relieved by rest and/or nitroglycerin
2. **Variant (Prinzmetal's) “rest” angina**
   - Coronary insufficiency due to **vasospasm** (which may be caused by endothelial dysfunction or damage & smooth muscle hyperreactivity) (Figure 3). Normal healthy coronary arteries cannot “spasm” or constrict to the point of producing ischemia.
   - Attacks often **occur during rest** (e.g. at night) when vagal tone is higher.
3. **Unstable angina (Acute Coronary Syndrome)**
   - Caused by platelet aggregation at fractured atherosclerotic plaques (Figure 3).
   - Often occurs at rest, and represents a change in the usual pattern of “typical” angina.
   - Symptoms are more intense & of longer duration (e.g. >20 minutes) than for “typical” exertional angina
   - Often degenerates into myocardial infarction (and is therefore considered a medical emergency).

The different forms of Angina represent 3 examples of ischemic heart disease:

Ischemic Heart Disease Classification

1. Chronic Coronary Artery Occlusion due to Atherosclerosis (**Typical or Exertional Angina**)
2. Coronary Vasopasm (**Prinzmetal's or Rest Angina**)
3. **Acute Coronary Syndromes**:
   - Ruptured Plaque & Platelet Aggregation (**Unstable Angina**)
   - Non-Transmural Infarct (**NSTEMI**)
   - Transmural Infarct (**STEMI**)

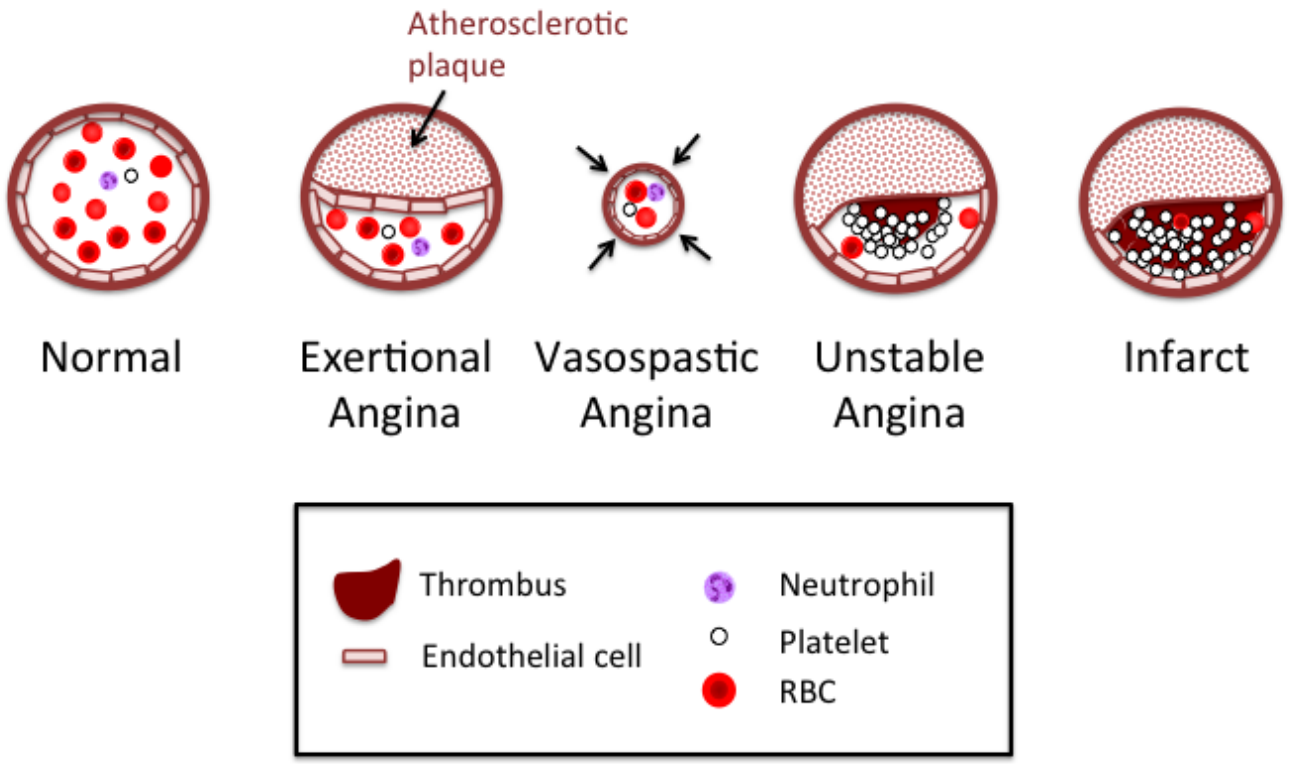

Figure 3. Coronary artery pathology. In stable (exertional) angina the arterial lumen is narrowed by the presence of a stable plaque, resulting in partial stenosis. In vasospastic angina, there is inappropriate vasoconstriction, resulting in intense vasospasm, commonly in the absence of a plaque. In unstable angina, a plaque rupture results in platelet aggregation and formation of a thrombus, resulting in subendocardial ischemia at rest. When a major coronary artery is completely obstructed by a thrombus, infarction or muscle death results. Adapted from Rhee et al (2011).

Drugs Used to Treat Angina

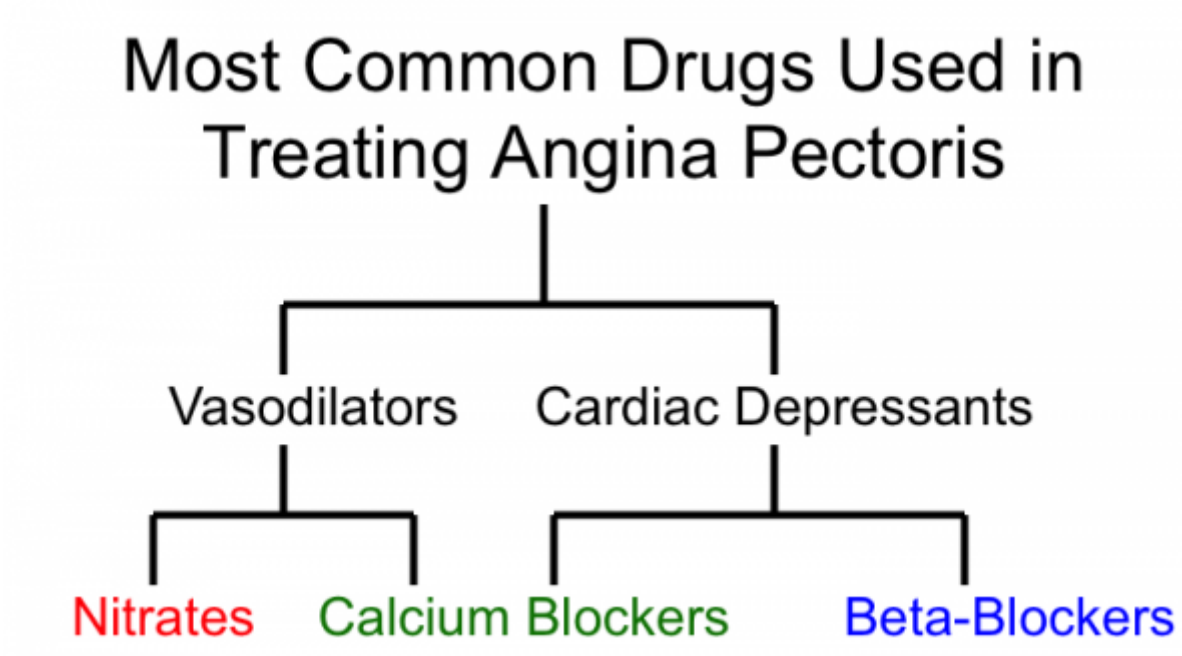

Figure 4. The 3 major categories of anti-anginal drugs & their primary therapeutic actions.

TABLE 1: CONTRIBUTING FACTORS & TREATMENT STRATEGIES FOR ANGINA	
Cause/Condition	**Treatment**
Vasospasm	Nitrates, Calcium Channel Blockers
Fixed Stenosis	Nitrates, Calcium Channel Blockers, β-Blockers, Angioplasty, Stents
Thrombosis	Thrombolytics, Antiplatelet Drugs
High Heart Rate	β-Blockers, Ca Channel Blockers
Increased Afterload	β-Blockers, Ca Channel Blockers, Antihypertensive Drugs
Increased Preload	β-Blockers, Ca Channel Blockers, Ranolazine

Organic Nitrates (Nitroglycerin)

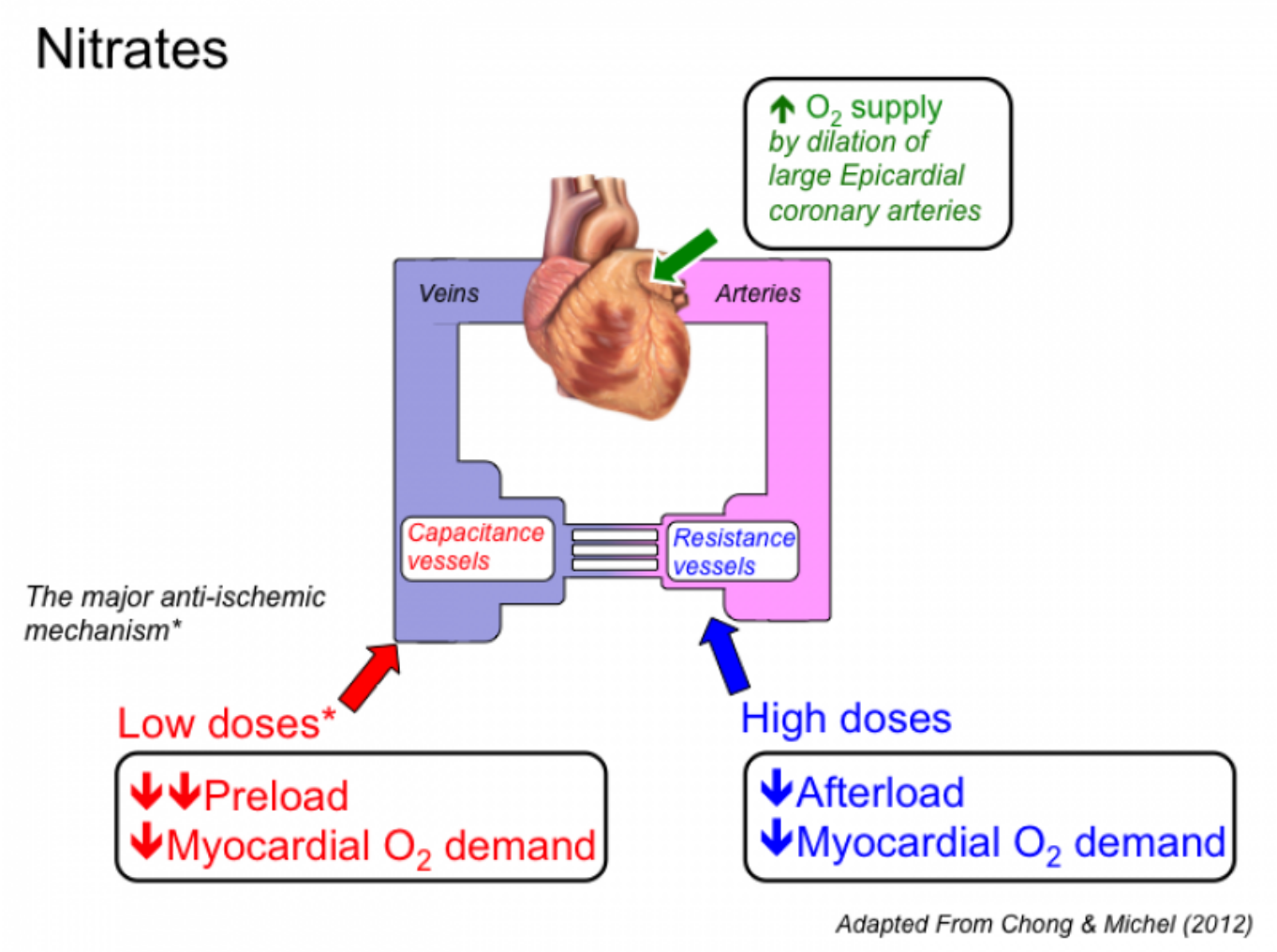

Figure 5. Nitrates such as nitroglycerin exert the majority of their therapeutic effects by causing "selective" venodilation (especially at low doses). Venodilation reduces the amount of blood returning to the heart, which results in decreased preload (decreased stretching of the heart at the start of systole). A decreased preload results in a decrease in the force of contraction during systole, and decreased work by the heart. Decreased work results in decreased oxygen demand. At higher doses nitrates also cause vasodilation of arterioles. This reduces the work of the heart by reducing the resistance the heart has to work against during systole (a decreased *afterload*). Nitrates have also been shown to dilated large epicardial coronary arteries, which can increase oxygen supply. However, the extent that coronary vasodilation contributes to the therapeutic effects of nitroglycerin

remains unclear.

Nitrate Mechanisms of Action:

1. **VENODILATION**
   - Venodilation is the primary effect produced by nitrates at low therapeutic doses. **Higher doses produce arterial vasodilation as well** (which can be therapeutic).
   - Nitrates such as nitroglycerin (NTG) are enzymatically broken down in the vascular wall by both glutathione S-transferase (GST) and mitochondrial aldehyde dehydrogenase isoform 2 (MtADH2) to release the vasodilator substance “nitric oxide” (NO)(Figure 6)(Zhang et al, 2009)
   - Enzymatic conversion of NTG to NO is greater in venous smooth muscle compared to arterial smooth muscle, which may account for the venoselectivity of NTG at low doses (Bauer & Fung, 1999)
   - Venodilation results in decreased “preload” (decreased ventricular chamber size, end diastolic volume, fiber tension) = decreased work by the heart
   - **Decreased preload & work of the heart results in decreased O_2 demand**, an effect which reduces ischemia (Figure 1)
   - Reduction of afterload (arterial resistance), a desirable therapeutic effect produced at higher doses can also produce reflex tachycardia (an unwanted side effect)

Other possible contributors to the mechanism of action for nitroglycerin are under investigation, and include:

1. **Redistribution of Coronary Blood Flow**
   - Nitrates can selectively increase collateral blood flow to ischemic areas (e.g. subendocardial regions)
   - Total coronary flow is not increased
2. **Reversal of Coronary Vasospasm**
   - Nitrates have been observed to increase flow in vasospastic angina
3. **Decrease in Platelet Aggregation**
   - Evidence for therapeutic significance is still weak

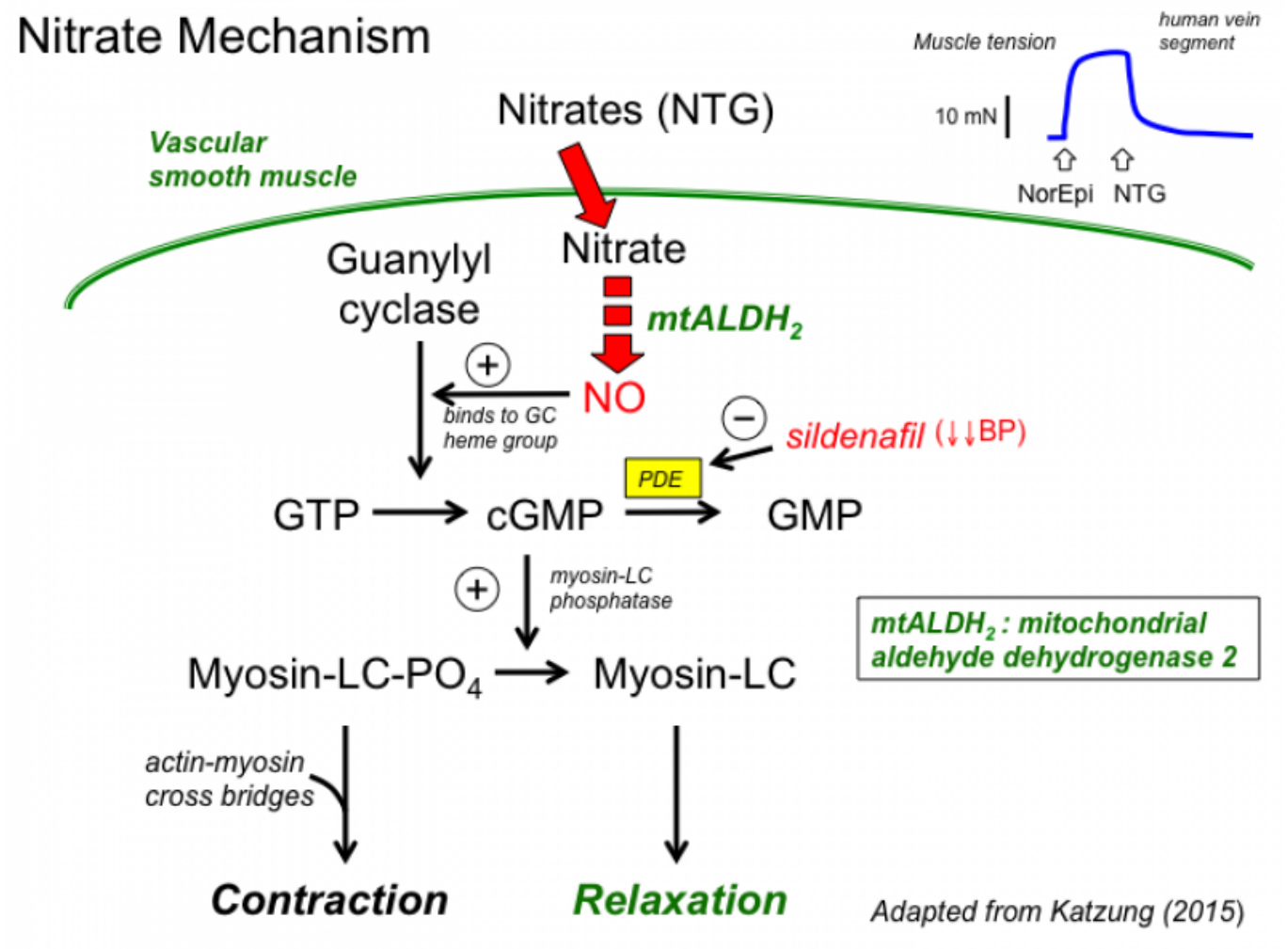

Figure 6. Mechanism of action of nitrates. Organic nitrates have the chemical structure RNO_2. The nitro group is reduced to form NO in by a mitochondrial enzyme (aldehyde dehydrogenase-2). Free nitrite is released, which is converted to NO. NO activates guanylyl cyclase (GC) by interacting with its heme group. Activated GC converts GTP to cGMP. cGMP activates a phosphatase which dephosphorylates myosin light chains, resulting in decreased interaction between actin & myosin filaments, and relaxation. cGMP is normally short lived due to metabolism by intracellular phosphodiesterase (PDE). Drugs such as sildenafil can inhibit PDE, resulting in a potentially dangerous intensification of the vaso-relaxant effect of nitrates. The inset (top right) illustrates the rapid onset of effect of nitroglycerin (NTG) on a segment of human vein that has been contracted by norepinephrine. Adapted from Figure 12-2 of Katzung (2015).

Use of Nitrates

- Acute Use:
  - **NTG is the mainstay of therapy for the IMMEDIATE RELIEF of angina**
  - the most common route of administration is **sublingual (tablets are placed under the tongue) which produces a rapid onset of effect, and avoids liver metabolism (no first pass effect) prior to reaching the systemic circulation**
  - duration of action is typically 10-30 minutes after a single dose
  - NTG is an unstable compound, and NTG tablets can lose their potency when exposed to heat, light or moisture, and have a limited shelf life. When this happens, typical NTG side effects, such as headache & dizziness are also diminished or lost.
- Prophylactic Use:

- dermal patches or slow release formulations of NTG and other similar nitrates are used for prolonged prophylaxis to reduce the incidence of angina
- tolerance develops with continual use (which can be reduced by having “nitrate free” gaps of ~8 hours at night

Nitrate Side Effects

- **Headache** (due to meningeal vasodilation)
- Dizziness
- **Reflex Tachycardia** (baroreceptor mediated due to a fall in arterial BP produced by higher doses of NTG)
- Orthostatic hypotension (less common)
- Tolerance
  - tolerance can be reversed by omitting dosing at night
  - “anginal rebound” episodes can occur during nitrate-free intervals

Nitrate Drug Interactions

- **Sildenafil & other Type 5 Phosphodiesterase Inhibitors (Erectile Dysfunction Drugs)**
  - **unsafe hypotensive episodes of >25 mm Hg** can occur if nitroglycerin is used within 24 hours after taking sildenafil (Viagra ®)(Cheitlin et al, 1999), or within 2 days after taking tadalafil (Cialis ®) (Cialis.com)
  - This interaction occurs because there is a low level of type 5 phosphodiesterase expressed in systemic arterial smooth muscle. When patients take nitroglycerin alone, cGMP levels in arterial smooth muscle are increased, resulting in a normally safe level of arterial vasodilation. However, when type 5 PDE has been inhibited by prior administration of a Type 5 PDE inhibitor, the vasodilator effect of the nitrate can be intensified to the point of potentially producing an excessive lowering of blood pressure that can precipitate a myocardial infarction & death

Beta Blockers

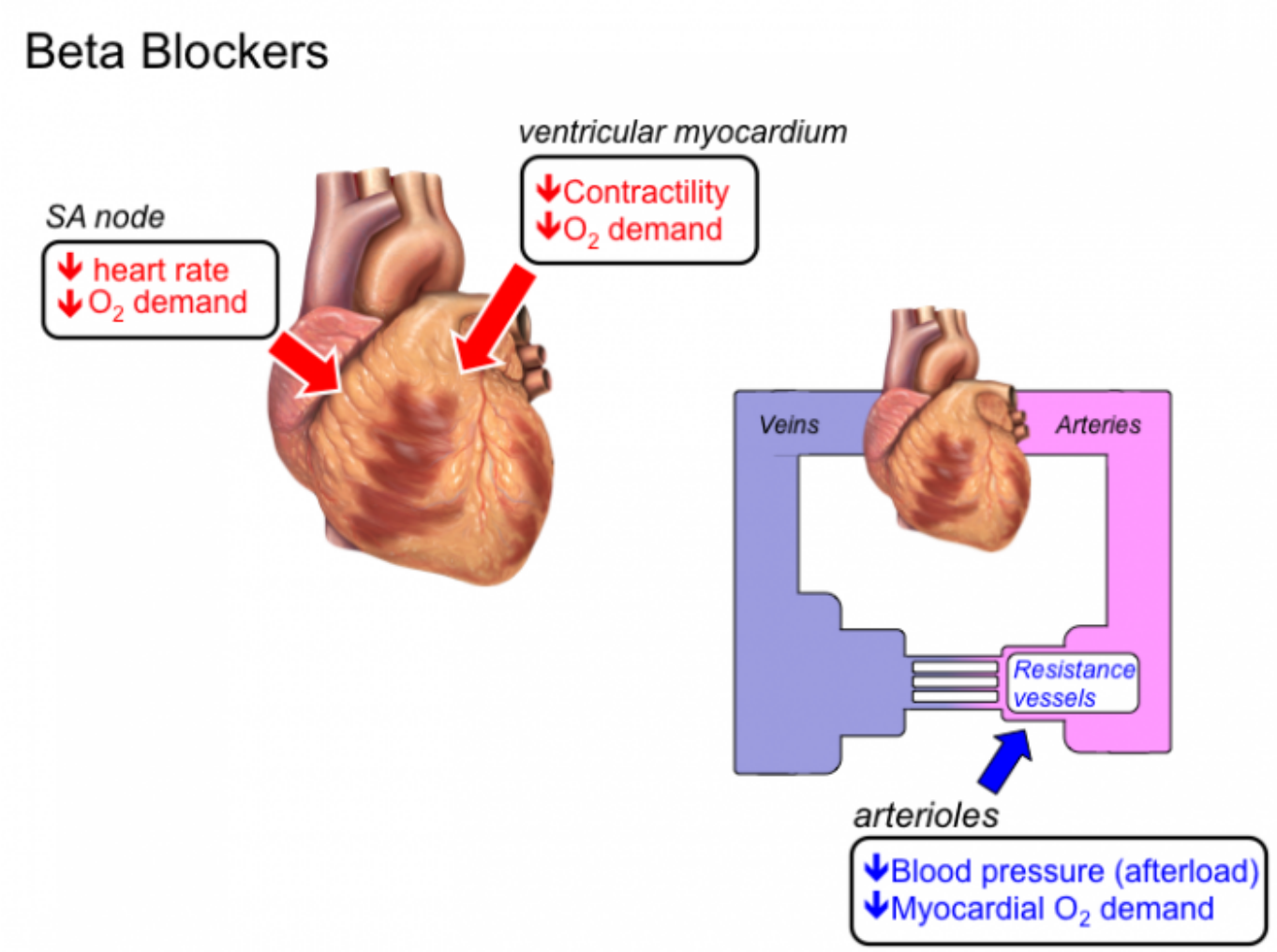

Figure 7 Sites of action of beta blockers in the treatment of angina. Beta blockers exert the majority of their effects on heart tissue by antagonizing beta-1 receptors (the subtype most heavily expressed in heart tissue). Beta blockers will block the effects of circulating and neuronal catecholamines, which have the greatest effect on heart rate and ventricular contractility. Reductions in both heart rate and contractility will reduce the work of the heart, resulting in a decrease in myocardial oxygen demand, which is "*anti-ischemic*". In addition, beta blockers also produce a reduction in total peripheral resistance, with an associated decrease in blood pressure & afterload. These effects also contribute to decreased work of the heart & myocardial oxygen demand.

FDA Approved Beta Blockers for Angina

- atenolol (Tenormin ®)
- metoprolol (Toprol XL, Lopressor ®)
- propranolol (Inderal LA ®)

Beta Blocker Mechanisms of Action:

- **REDUCED OXYGEN CONSUMPTION** (O_2 demand) due to:

1. reduced heart rate (especially during exercise)
2. negative inotropic effect
3. reduced blood pressure (especially systolic) during exercise; beta blockers reduce TPR

Beta Blocker Use:

- **ONLY** used for **PROPHYLAXIS of EXERTIONAL ANGINA**.
- **Adding a beta blocker to a patient's drug regimen for exertional angina can reduce the need for nitroglycerin PRN by decreasing myocardial work and oxygen demand (by reducing heart rate, contractility, and afterload) that contribute to producing angina (Figure 1).**
- **BETA BLOCKERS** are considered **INEFFECTIVE, or CONTRAINDICATED for VARIANT (VASOSPASTIC) ANGINA** (it may worsen such attacks by blocking some β_2 receptors that produce vasodilator effects, leaving α-mediated effects unopposed (Figure 8)(Robertson et al, 1982).
- Even β_1 selective blockers will block some percentage of β_2 receptors as dosage is increased, due to less than perfect selectivity.
- β blockers should also be avoided if the chest pain or ischemia is likely to have been caused by **cocaine** for the same reason (leaving the α-mediated coronary vasoconstrictive effects of catecholamines unopposed)

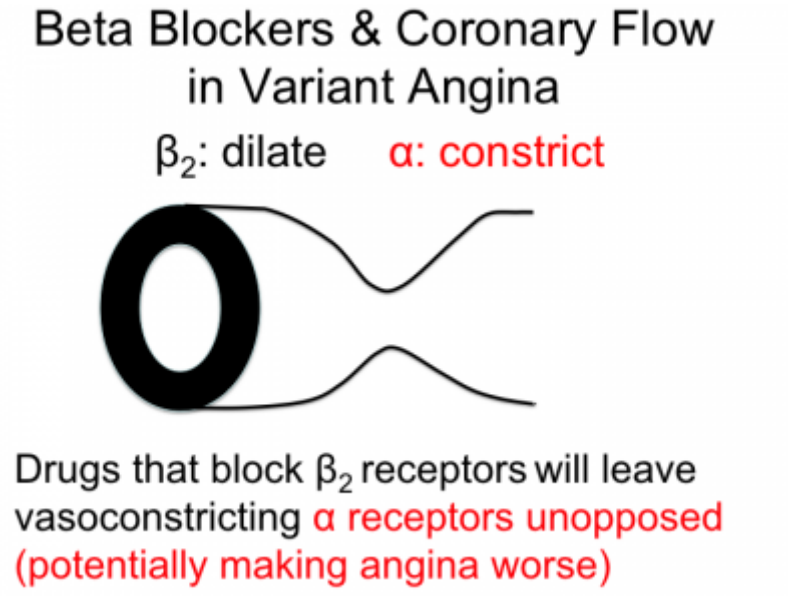

Figure 8. Proposed mechanism for undesirable effect of beta blockers in variant angina. Beta blockers may block coronary β_2 receptors, leaving α-mediated vasoconstrictor effects unopposed.

Beta Blocker Side Effects:

- Increased End Diastolic Volume (increases preload, which ↑O_2 demand)
- Increased Ejection Time (↑O_2 demand)
- Fatigue
- Insomnia
- Erectile dysfunction
- Avoid use in patients with:
  - asthma (bronchospastic disorders)
  - depression
  - SA nodal or AV nodal disease (bradycardia)
- Sudden discontinuation can intensify ischemia (due to ↑expression of β receptors, rebound tachycardia & ↑afterload)

Treatment of Beta Blocker Overdose:

- in 2007 the Annual Report of the American Association of Poison Control Centers (AAPCC) National Poison Data System reported 9291 toxic exposures to beta blockers (Emedicine.Medscape.com)
- Propranolol is the most toxic beta blocker (due to its nonselectivity) and is the most frequently used in suicide attempts
- The preferred treatment is to increase cardiac output by increasing contractility & heart rate (or both) using:
  - **GLUCAGON** (which has its own cardiac receptors & increases intracellular cAMP)
  - **Epinephrine + atropine** (if glucagon is not available); epinephrine must competitively overcome the effect of the beta blocker on β_1 receptors to produce a beneficial effect in this setting.

Calcium Channel Blockers

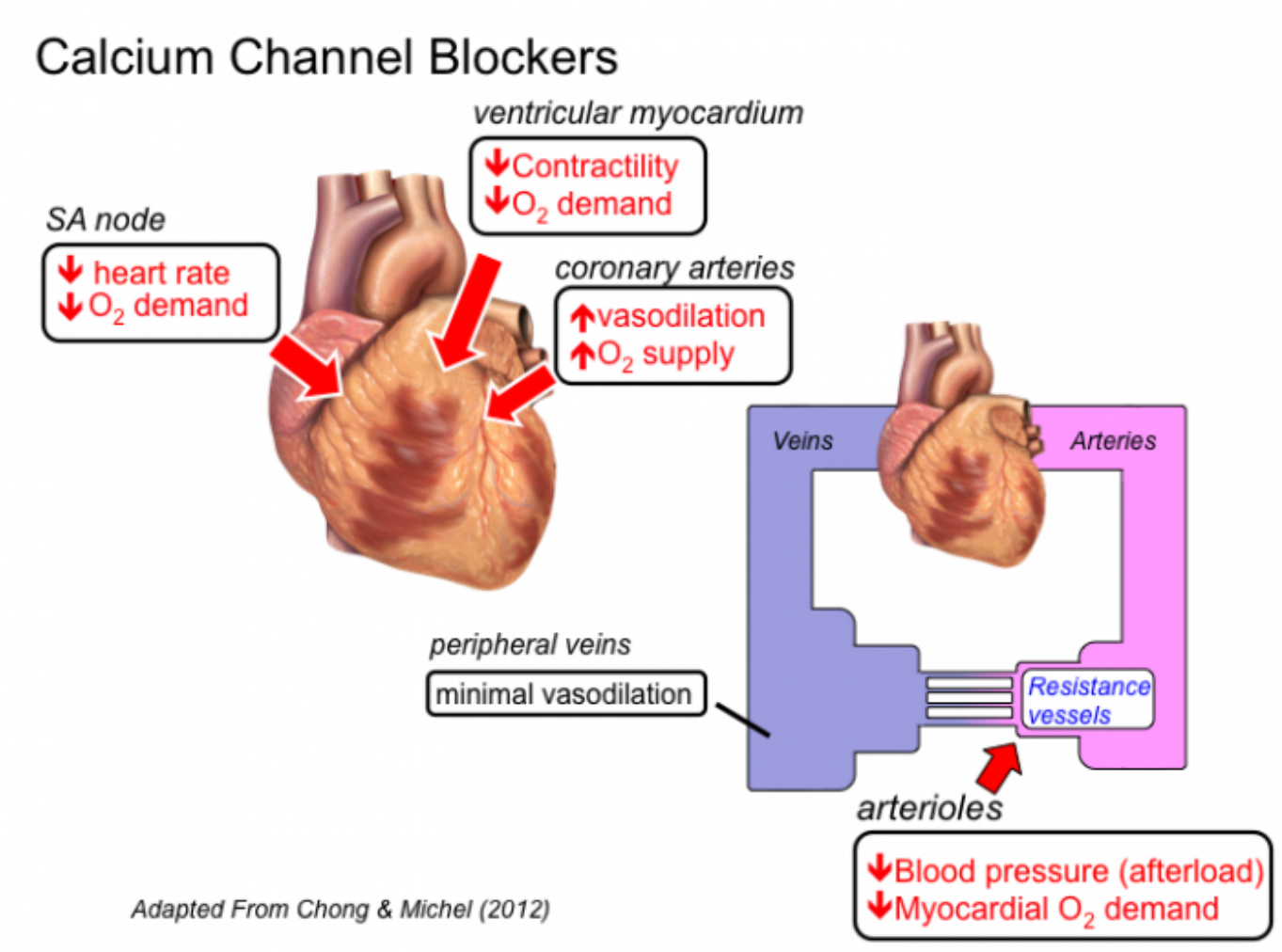

Figure 9. Sites of action of L-type calcium channel blockers in the treatment of angina. Calcium channel blockers reduce calcium influx in all areas of the heart, resulting in reduced heart rate & ventricular contractility. Reductions in both heart rate and contractility will reduce the work of the heart, resulting in a decrease in myocardial oxygen demand, which is "*anti-ischemic*". Calcium channel blockers also cause coronary artery vasodilation, which can increase oxygen supply. In the peripheral circulation, calcium channel blockers also produce a reduction in total peripheral resistance, with an associated decrease in blood pressure & afterload. These effects also contribute to

decreased work of the heart & myocardial oxygen demand.

FDA Approved Calcium Channel Blockers for Angina

- amlodipine (Norvasc ®) - vascular selective dihydropyridine
- diltiazem (Cardizem ®)
- nifedipine (Procardia ®) - vascular selective dihydropyridine
- verapamil (Calan ®)

Calcium Channel Blocker Mechanisms of Action:

1. Block calcium influx through voltage gated L-type Ca channels in both cardiac & vascular smooth muscle
2. REDUCED OXYGEN CONSUMPTION (O_2 demand) due to:
   - ↓heart rate
   - ↓contractility
   - ↓afterload (↓TPR & BP) - with little effect on venous resistance
3. INCREASED CORONARY BLOOD FLOW (especially useful for vasospastic angina)

Calcium Channel Blocker Side Effects:

- constipation
- flushing & dizziness
- AV & SA node depression (more common with verapamil)
- **dihydropyridines can cause reflex sympathetic stimulation of the heart** due to their vascular selective effects (which if significant can make them less effective as monotherapy vs diltiazem or a beta blocker); combining them with a beta blocker can overcome this unwanted side effect.

Ranolazine

- New alternative drug for patients who can't tolerate other antianginal drugs
- Mechanism: shortens cardiac action potential by blocking a plateau Na current. This indirectly **decreases Ca influx by abbreviating phase 2**, thereby producing a negative inotropic effect, which decreases O_2 demand
- Higher doses increase the QT by blocking IK_r (which is arrhythmogenic)

Useful Drug Combinations

Nitrate + β blocker

- different mechanisms of action can produce additive efficacy, as well as reduce each others unwanted side effects:
- The effects of a **β blocker prevents reflex tachycardia & positive inotropy** produced by nitrates
- Adding a **nitrate can reduce the increase in End Diastolic Volume** caused by β blockers by

increasing venodilation (increased venous capacitance)

Calcium Channel Blocker + β blocker + Nitrate

- These drugs can produce additive effects by different mechanisms
- A calcium channel blocker may cause improvement if there is a vasospastic component causing angina
- However, caution should be used to avoid lowering BP & heart rate excessively (coronary arteries need perfusion pressure to function properly!)

Emergency Department Treatment of Patients with Chest Pain

There are 4 variables affecting myocardial damage:

1. area of heart supplied by the occluded vessel
2. myocardial oxygen demand
3. oxygen supply
4. collateral circulation in the affected area

MONA

MONA always greets patients with chest pain at the door!

- **Oxygen** (nasal or mask) to limit ischemic injury; reduces ST elevation
  - **Current AHA guidelines: oxygen therapy is indicated only if hemoglobin oxygen saturation is below 90%** (see boxed discussion)(Amsterdam et al, 2014).
- **Aspirin** (325 mg dose, chewed) to reduce platelet aggregation
- **Nitroglycerin** (sublingual) produces coronary dilation, decreases preload & afterload to reduce O_2 demand
- **Morphine** (i.v.) to reduce pain & anxiety, which indirectly decreases O_2 demand by affecting heart rate, blood pressure & contractility
- Also:
  - β-blockers if heart rate is high (and ischemia is not likely caused by vasospasm)

Concerns about Oxygen Therapy

There is a current debate concerning whether oxygen therapy is beneficial or harmful. As a result, the current AHA clinical guidelines recommend its use only when oxygen saturation falls below 90% (94% was the recommended threshold in ~2010). In theory, oxygen therapy could either beneficial or harmful. **Potential Benefits**: oxygen therapy may increase myocardial oxygenation and decrease infarct size. **Potential Harm**: oxygen therapy may decrease cardiac blood flow and perfusion, reduce cardiac output, and increase coronary

vascular resistance. In addition, if myocardial reperfusion occurs following a period of prolonged ischemia, oxygen may have a paradoxical harmful effect by increasing the levels of oxygen free radicals, resulting in enhanced reperfusion injury (O'Connor et al, 2010).

Unstable Angina

- **Caused by platelet aggregation** (and not a fibrin containing thrombus)

Rx Unstable Angina

- **MONA**
- **Heparin** (antiplatelet)
- Additional antiplatelet drugs may be needed (e.g. clopidogrel or IIb/IIIa inhibitors)
- β-blockers to reduce O_2 demand if heart rate &/or blood pressure is high (calcium channel blockers in refractory patients)
- Angioplasty, stents
- Statin therapy initiated before discharge from the hospital (Aroesty et al, 2018)

Differing Usefulness of Clot-Busting Fibrinolytics in Unstable Angina, NSTEMI & STEMI

Unstable angina is a medical emergency that can rapidly evolve into a myocardial infarction with or without an associated ST elevation in the ECG. **Fibrinolytics have been found to be of benefit only in those myocardial infarctions associated with an ST elevation (STEMI)**. A brief explanation of this observation is summarized below.

- Unstable Angina:
  - **patients with unstable angina do not benefit from fibrinolytic therapy** because the cause for their condition is **platelet aggregation *vs* formation of a fibrin clot**.
- STEMI:
  - complete occlusion of a coronary artery by a fibrin containing thrombus will produce ST elevation in the appropriate leads of the ECG in the early stages of a myocardial infarction. This is commonly referred to as an **ST E**levated **M**yocardial **I**nfarction (**STEMI**).
  - **treatment with fibrinolytics (e.g. tPA) in the early hours of an evolving STEMI restores blood flow in most occlusions (70-80%), and reduce mortality by ~50%.**
  - Other treatment options include angioplasty, insertion of a coronary stent, and coronary artery bypass surgery.
- NSTEMI:
  - a 'Non'-STEMI (NSTEMI) is a myocardial infarction where ST segment elevation is not observed
  - NSTEMIs are believed to be caused by partial occlusion of a coronary artery by differing amounts of clotting proteins and platelets than occur in a STEMI (Amer Coll Cardiol, 2013).
  - **Fibrinolytics can produce serious unwanted outcomes (e.g. excessive bleeding)**, and the results of several clinical trials argue AGAINST the use of clot-busting fibrinolytics in treating

NSTEMI or unstable angina (Simons, 2012; Amer Coll Cardiol Guidelines, 2013).

SUMMARY

Angina of Effort

- The drug choice depends upon a patient's response & co-morbid conditions (e.g. hypertension, AVN block, asthma, depression)
  - Calcium Channel Blockers
  - β-blockers
  - Nitrates

Vasospastic Angina

- Calcium Channel Blockers
- Nitrates
- Combination of Nitrates & Calcium Channel Blockers
  - Combinations abolish angina in ~70%, marked reduction in another ~20%
- NOT β-blockers

Unstable Angina

- **MONA**
- Heparin
- Beta Blocker (if HR is high)
- Clopidogrel or IIb/IIIa inhibitors if needed
- Calcium Channel Blockers in refractory patients
- Angioplasty, stents
- Statin therapy should be initiated

Ready for A Self Assessment Quiz?

- **Treatment of Angina** (10 Qs)

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